Chapter 1

General introduction and aims. Juvenile idiopathic arthritis: more than just a joint.

Wineke Armbrust

PART I: MEDICAL BACKGROUND OF JUVENILE IDIOPATHIC ARTHRITIS.

Introduction

Juvenile idiopathic arthritis (JIA) is a heterogeneous group of autoimmune diseases affecting one or more joints. An autoimmune disease is characterized by the presence of autoantibodies or autoreactive T-cells. Autoimmunity is in fact present in everyone and is usually harmless unless it progresses to become a harmful disease like JIA (1). JIA is defined as arthritis with a duration of more than 6 weeks occurring before the age of 16 years. Typical presentations of children with JIA are symptoms caused by chronic arthritis such as: limping, morning stiffness, functional disabilities, and a deflection of motor performance (2). In more severe cases, weight loss, malaise, contractures, and mild fever can be present (3).

More than 100 years ago in 1891, M.S. Diamantberger, an assistant at the Hôpital Rothschild in Paris, was intensively involved with young patients with arthritis. Diamantberger proved for the first time that there are three totally different types of courses in children, and particularly mentioned the form affecting the internal organs and the eyes. This was the theme of his dissertation, which was first made public in 1890 and was published in 1891. In his dissertation, he had in fact described the so-called systemic form six years before Still and had anticipated oligoarthritis accompanying inflammation of the eye (4). However, in 1897, it was Dr. Still who officially gave his name to the form of arthritis accompanied with systemic symptoms like lymphadenopathy, rash, and spiking fever now known as systemic JIA (5). After this first publication, several publications appeared in the mid-twentieth century, which dealt with the classification and treatment of juvenile arthritis. Even at that time the need for psychosocial care was already recognized.

“A practical classification of the disease process is recommended as mild, moderate or severe depending on the duration of the disease, the degree of joint involvement, constitutional reactions and the degree of residual joint deformity. Treatment is difficult but several procedures have proven to be essential. Complete bed rest is the most important part of treatment” (6). “A program for the management of Juvenile Arthritis should permit the child an optimal developmental experience despite the persistence of potentially crippling inflammatory disease. Drugs are useful, although no more than palliative and all are significantly toxic. The emotional, social and educational needs of the child with such a chronic disability deserve most thoughtful attention” (7).

In the past two decades our knowledge of its pathogenesis and treatment options has advanced markedly, resulting in better outcomes regarding remission and the prevention of damage in patients with JIA. A joint effort spanning European and American has resulted in different medical protocols in order to improve treatment regimens. However, diagnostic tools and protocols on psychosocial constraints are lacking, as are interventions or coaching programs for patients, which deal with psychosocial barriers.

Pathogenesis of JIA

The cause of JIA is unknown and assumed to be multifactorial. Genetic associations have been shown to contribute to a susceptibility for developing the disease (8). For the onset of arthritis, a sequence of events is needed in genetically predisposed individuals; a series of hits may result in a break in immunological tolerance, leading to clinical signs of active disease (9). Although the exact nature of these hits is unknown, they are thought to initiate the inflammatory response, leading to T-cell proliferation, the production of pro-inflammatory cytokines, and the inhibition of anti-inflammatory processes (10,11). Soon after the induction of the autoreactive response, irrespective of the trigger, almost all elements of the immune system are involved in the immune response (Figure 1) (12).

For a long time it was thought that regulatory T cells (Treg) play an important role in limiting and reversing the autoimmune response, and that a deficient function or low number of these Tregs resulted in ongoing disease or a relapsing disease course (13). More recent studies have shown that, in addition to an impaired Treg response, effector T cells can become refractory for suppression, especially in a pro-inflammatory environment (14).

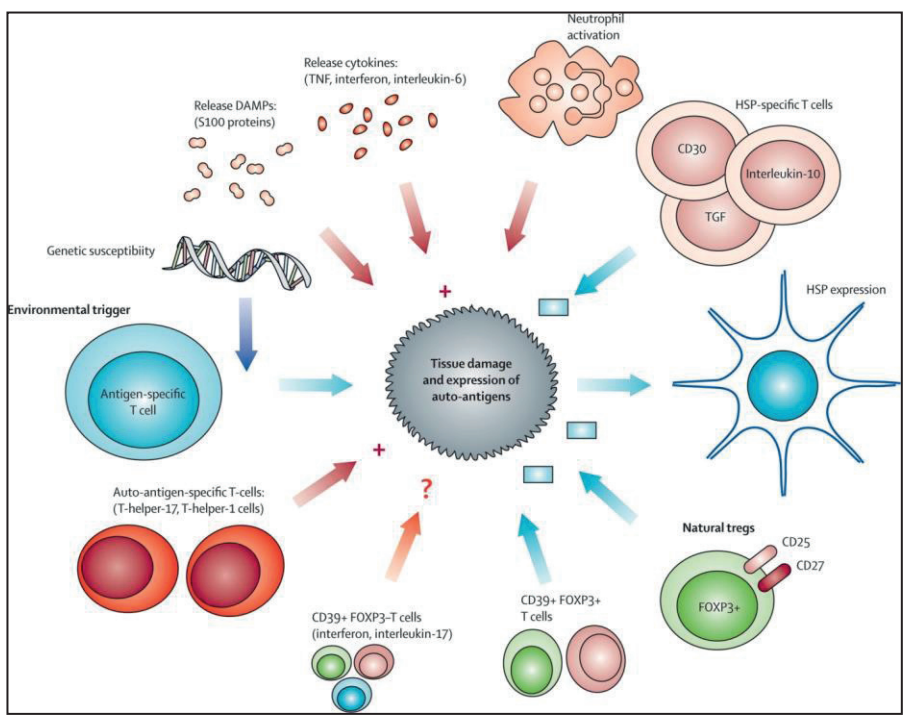

Figure 1. The balance between tolerance and inflammation in juvenile idiopathic arthritis
In a genetically susceptible individual, an environmental trigger leads to local tissue damage, the expression of autoantigens (such as heat shock proteins), and inflammation, which activates a range of innate and adaptive immune responses that can either down-regulate (blue arrows) or promote (red arrows) local inflammation. DAMPs=damage-associated molecular pattern molecules. HSP=heat-shock protein. TGF=tumor growth factor. TNF=tumor necrosis factor. (Prakken et al. Lancet 2011(12) with permission)

Disease assessment

Much effort has been made in the past few years to assess the disease clinically, using imaging techniques and development of new biomarkers. In 2001, the ILAR (International League of Associations for Rheumatology) developed classification criteria for JIA, which were revised in 2004 (15). Within JIA, 8 subtypes were distinguished, based on the number of affected joints, laboratory parameters, and extra articular manifestations. Recent studies have shown that the systemic form of JIA is an acquired autoinflammatory rather than an autoimmune-mediated disease, because autoantibodies and autoreactive T cells are absent (12). The ILAR criteria made it possible to distinguish different types of JIA, and enabled more uniformity in clinical care and also in research.

From that point on, criteria for disease activity were defined as remission, and high, low, and moderate disease activity (16,17). Remission implies a complete lack of disease activity as defined by Wallace and colleagues; no arthritis, no systemic symptoms, no uveitis, and the lowest physician global assessment possible on a scale (16). For the scoring of disease course (improvement or deterioration) in daily practice and for research purposes, the ACR-Pedi was developed comprising physical global assessment of disease activity, patient/parents score on overall well-being, functional ability, number of joints with active arthritis, number of joints with limited motion, and the erythrocyte sedimentation rate (ESR) (18). Improvement was defined as an improvement of more than 30% on 3 out of the 6 items, with no more than one of the remaining variables deteriorating with >30% (18). However the nature of this tool does not enable the measurement of actual disease activity or absolute improvement. For this purpose the juvenile arthritis disease activity score (JADAS) was validated, comprising a physician global assessment of disease activity, parent/patient global assessment of well-being, and active joint count, with or without ESR (19,20). The JADAS also includes cut-off points for remission, and low and high disease activity of the different subtypes of arthritis.

In addition to clinical scoring methods, imaging is becoming increasingly important in assessing disease activity and monitoring the disease course. The great challenge in the use of the new imaging techniques is to be able to distinguish abnormalities in the context of JIA from the normal development of the growing musculoskeletal system. The Pediatric Rheumatology European Society (PRES) and the European League Against Rheumatism (EULAR) recently published points to consider for the use of imaging in the management of patients with JIA (21).

In addition to clinical and radiological scoring of the disease activity, biomarkers have aroused great interest as predictors of the disease course, severe or mild phenotypes, response to treatment, and disease-related complications. At the point of writing, the ideal biomarker has not yet been discovered that is able to give a clear prediction about the severity of the disease, response to therapy, and the chance of remission or a relapsing course. Furthermore, treatment cannot be targeted, based on the type and level of different biomarkers.

Treatment of JIA

Current insight shows that achieving remission in an early stage of the disease predicts better long-term outcome (22-26). Until the 1990s, NSAIDS (acetyl salicyl acid),

corticosteroids, hydroxychloroquine and gold were used with much limited success and significant side effects. With the introduction of Methotrexate (MTX), a disease modifying anti-inflammatory drug (DMARD), in 1992, an important step forward in treatment was made (27). The prognosis of JIA improved significantly; more than 70% of patients showed an improvement on the ACR-Pedi 30% after introducing MTX, and long-term damage was reduced (28). Ten years after the introduction of MTX for the treatment of JIA, Etanercept was approved for resistant polyarticular JIA in the Netherlands. Etanercept, a biological DMARD that inhibits the effect TNF-alpha, was effective in 74% (ACR-Pedi 30%) of the patients who failed with MTX, and short-term use was proven to be safe (29). From then on, other biologicals were approved for non-systemic JIA, targeting other elements of the immune system, for example, medications targeting IL-6 or co-stimulatory molecules. These newly introduced biological DMARDs have proven to be as efficacious and safe as Etanercept (30). For S-JIA, the introduction of IL-1 blockade has led to a spectacular improvement in prognosis. Eighty-five percent reached remission or near remission, whereas in the pre-biological era more than 60% of patients showed persistent disease activity and needed medication, in this case, steroids (31).

With the growing number of possible treatment regimens, the American College for Rheumatology has issued guidelines for the treatment of systemic and non-systemic JIA (32,33). The European Agency for Health has supported an initiative called SHARE (acronym for Single Hub and Access point for pediatric Rheumatology in Europe), aimed at providing European countries with recommendations for the care of children and young adults with rheumatic diseases (34). These guidelines are expected to be completed in 2016. Based on these guidelines, an evidence-based Dutch guideline is in development, adjusted for local practices and, most importantly, with input from the patients board.

Medical outcome

Many patients and their parents would like to believe that the word juvenile in JIA means that a miracle happens in puberty, making the disease disappear. As physicians, we wish that this magic recovery would always be a reality, but this dream only applies to a certain percentage, assumed to be 60%, of patients. Many efforts have been made to measure and predict long-term outcome, but one obstacle in assessing long-term prognosis is that patients who outgrow their arthritis are mostly lost to follow-up, which results in a certain bias. We do know that almost no patients have any functional disabilities or disorders in movement patterns at 17 years follow-up (23). In addition to the direct musculoskeletal consequences of JIA, there is growing evidence that patients with JIA are at risk for atherosclerosis, obesity, and a diminished bone-mineral density long term (35-38).

How current treatment regimens will affect the long-term psychosocial outcome is not yet known. It is in this regard that there is a need to include patients' views on their disease and the outcome in routinely assessed disease activity scores, as just mentioned

PART II: PATIENT-REPORTED OUTCOMES AND PARTICIPATION

Introduction:

Patient-reported outcome measures (PROMs) provide insight into perceptions by patients. PROMs are of growing importance in the clinical management of patients with pediatric rheumatic conditions and are included as outcome measurements in clinical trials more frequently (39,40). PROMs basically include 3 domains: physical health, mental health, and social health. Physical health refers to symptoms and physical functioning, mental health to affect behavior and cognition, whereas social health includes relationships and social functioning (39). In patients with JIA pain, fatigue, disability, HRQoL, and side effects of the medication are well-known patient-reported outcomes.

PROMs, in terms of side effects of medical treatment, have revealed a downside to MTX; half of the patients using MTX suffer from intolerance for this medication, which is a symptom complex like anticipatory and associative complaints, indicating that classical conditioning plays an important role (41). In some cases this intolerance leads to stress and low therapeutic adherence. Some daily examples from the field are: "Previously yellow was my favorite color, but, since the MTX was started, I feel sick wearing my yellow t-shirt, because it reminds me of MTX." MTX has a distinct yellow color. "Fried potatoes were my favorite meal on Friday, but since I have to take my MTX on Friday I have to throw up even from the smell of fried potatoes." "After my daughter started with the MTX, all the plants in the living room died; the other day I found out that she was throwing the pills into the flowerpots." The benefits of the biologicals are impressive, but all these medications are administered parenterally, causing procedural stress in some cases. In daily practice, route of administration or nausea constitute important factors for low adherence and for the adjustment of the medication; however, these PROMs are not included in current treatment regimens.

These observations from daily practice contrast with results of a study that examined the preferences of parents regarding the drug treatment of their child. Parents rated side effects as less important; they wanted to target the treatment to the reduction of pain and improvement of daily functioning (42). The goal of physicians, on the other hand, was to reach remission and to offer the child a safe drug regimen with a minimum of side effects (43). Patients' perspectives regarding treatment preferences for arthritis has not been studied widely. In one study, 9 patients were interviewed about which clinical features were the most important during the disease course. Patients indicated pain, side effects of the medication, active joints, and HRQoL as important issues (43). To enhance compliance, it is necessary to understand how patients evaluate the medication and side effects. A good example of the strength of patient participation is structured patient interviews on best-worse scaling of new drugs and side effects, as was done in patients with Duchenne muscular dystrophy (44).

In addition to patients' judgments concerning the medication regimen, it is less clear how patients perceive their health, abilities, and their HRQoL, and it is unclear which factors contribute to disability and a perceived impaired health status in one patient, while other patients with the same condition live an unrestricted live. In order to be able to support patients in living with JIA, the factors need to be revealed that contribute to an

optimal feeling of health, maximum functioning, and that restrict the feeling of disability. These factors should be a target in the treatment, in addition to attaining remission, limiting side effects, and preventing damage.

International classification of functioning, disability, and health (ICF)

To study patient-reported outcomes on health and disability, one needs to define these concepts. Until recently, health was seen as the opposite of death or disease.

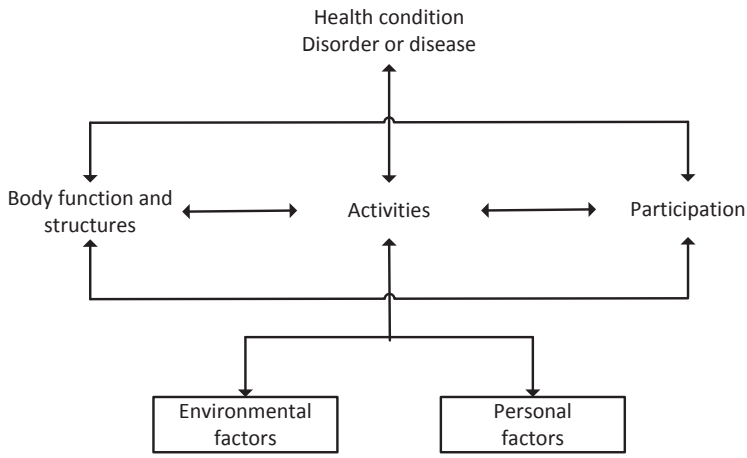

Figure 2. Interactions between the components of ICF

Disability was seen as a medical issue of a bodily impairment such as blindness, deafness, or as a restriction hindering an individual from participating in activities, for example. In 2001, the World Health Organization (WHO) developed the ICF, by which self-reported health can be classified, which consists of four domains: body structure; body function; activity, participation and environmental factors. (Figure 2) (45). The purpose of the ICF is to create an integrated bio-psychosocial model of health status and to reveal all factors contributing to impairments of one or more of the four domains. In patients with JIA, many factors play potentially negative roles on one or more domains. For example, daily discomfort, such as pain, stiffness, fatigue and mood disturbances, is present in a major portion of patients, and is thought to affect participation and carrying out activities (46-49).

Physical disability

In 1949, the Committee for Therapeutic Criteria of the New York Rheumatism Association, chaired by Steinbrocker, published criteria for functional impairment, ranging from Class I, meaning no impairment, to Class IV, indicating totally incapacitated (50). Regarding the improved treatment regimens resulting in low long-term damage, the Steinbrocker criteria are no longer appropriate for judging outcomes in patients with JIA.

The PRINTO network of pediatric rheumatology centers has validated the Childhood Health Assessment Questionnaire (CHAQ). This instrument measures functional impairment in nine domains, with scores ranging from 0 to 3, where 0 stands for no impairment and 3 for maximum impairment. The CHAQ was translated into many languages including Dutch (51,52); this was an important step in recognizing functional ability as an outcome parameter in pediatric rheumatology. Functional ability became an essential outcome measurement in clinical trials as an indicator of success of treatment regimens. However, the perceived functional ability of the patients, or as judged by the parents, is impaired; often the patient's evaluation does not correlate with the opinion of the physician regarding the physical ability of the patient (53). In addition, functional disability may not correlate with disease activity or joint damage but with the patient's perception of pain and fatigue (54). So the interpretation and consequences of impaired functional ability, as assessed by the patient or parent, needs to be reconsidered.

Pain

In 1961, the first study concerning pain in JIA was published by Laaksonen and colleagues (55). Pain in children with arthritis was compared with pain in adults with arthritis. In this study, it was observed that children with arthritis did not experience as much pain as adults with affected joints. Based on this difference, the authors readily concluded that pain was comprised of a physical and mental component. In another study in 1977, pain was simply measured with a Visual Analogue Scale, and the result did not correlate with disease activity as assessed by the physician, based on joint count, ESR, and functional status. Therefore, the conclusion was drawn that pain could not be used to monitor disease activity in patients with JIA (56). In 1987, all possible factors related to pain experience and expression in patients with JIA were covered in a comprehensive model (57). Several family, environmental, and child psychological factors were found to interact with disease-specific parameters in determining pediatric pain perception and report. A multidimensional age-appropriate assessment model was suggested for use in further examination of pediatric chronic and recurrent pain (57).

Pain is frequent in patients with JIA; patients report moderate to severe pain more than 60% of all days, and they tend to use more pain relief medication compared to healthy peers (47,49,58,59). The cause of pain in patients with JIA is a complex interaction between physical and psychosocial determinants. Pain thresholds decrease with JIA at the time of active disease and tend to remain lowered long after remission has been reached (60-63). Surprisingly, decreased pain thresholds do not correlate with the sense of pain as reported by the patients, suggesting that the experience of pain in patients with JIA reflects a multifactorial cause (61). At the onset of disease, the disease activity accounts for 28% of the reported pain (64), whereas this is only 2% in longstanding JIA cases (65). In patient-reported outcome studies, pain has been demonstrated not to be correlated to disease activity (66-68), but it did correlate with depressive symptoms (69,70) and an impaired health-related quality of life (71). Pain can prevent children from being active (58), and it is one of the major factors, on which patients and parents base reports on current state of the disease (66,72).

Fatigue

There are only a few studies on fatigue in JIA, and its causes and implications are poorly understood. Nevertheless fatigue is common; more than 60% of patients with JIA suffer from fatigue (48,73). Fatigue is highly associated with increased pain, low functional ability, and a reduced Health-related Quality of Life (HRQoL) (48,74). Similar to pain, fatigue is not convincingly correlated with disease activity (47,48,73,75). The consequences of fatigue for daily functioning have not been thoroughly studied.

Psychosocial functioning

JIA is an unpredictable disease that might lead to uncertainty, a disrupted sense of normality, and impaired social participation (76,77). In fact the patient does not know how the next day or week will be, due to fluctuations in disease symptoms. Patients with JIA often feel depressed, anxious, and are frustrated about suffering from a chronic disease. These emotions are correlated with perceived physical impairment more than with disease severity (59,69,78-80).

Suffering from JIA has consequences for the patient's self-esteem, self-concept, adjustment at school, general well-being, and has evoked disturbed parent-child relationships that range from significantly hampered (81-83) to remarkably similar to case controls (84). Self-esteem is often referred to as an individual's self-perception of his/her skills, abilities that motivate specific cognitive processes and behaviors (85). In patients with JIA, self-esteem is impaired as a result of emotional problems (82), whereas in adults with RA lower self-esteem leads to higher stress and greater symptom severity in daily life (85).

Body image encompasses body-related self-perceptions and self-attitudes such as body satisfaction and dissatisfaction (86). In young patients (82) as well as in adults (65,83) with JIA, body image is disturbed compared to healthy controls. In the past, growth disturbances such as micrognathia could cause impaired body image, which is rarely seen nowadays. But still, patients feel different compared to their peers due to pain, fatigue, feeling disabled, and suffering from nausea as a side effect of the medication (76). These negative experiences can make patients feel negative about their bodies. Despite these negative consequences, patients are capable of entering into sexual and other relationships (87,88), although patients often report disease-related difficulties in their sexual contacts (65,77). Regarding these potential negative effects from JIA, children and adolescents seem at no risk for long-term psychological problems (89); however, long-term follow-up studies are sparse.

School attendance is important for social functioning and personal development. Studies on school attendance and social functioning are not unambiguous. In a report of a small group of JIA patients, school absenteeism was found in more than 30%, leading to a negative effect on schooling (90). Other studies show normal school attendance and occupational outcome in children and adolescents with JIA (91,92). Daily physical symptoms and mood could be predictors of school participation and social activities (47,49). An important study of Foster and colleagues (2003) showed an excellent educational level among young adults with JIA but a higher rate of unemployment compared to healthy peers (93). The cause of this lower employment rate in JIA is so far unknown.

Physical health

The exercise capacity (EC) and the physical activity (PA) level are significantly lower compared to healthy peers, and these two physical outcome parameters are moderately correlated (94–97). PA levels and EC do not return to normal, as compared to healthy peers, after remission has been reached (94–96). PA cannot be predicted by disease duration or functional ability (98), although severe hip or ankle involvement is related to lower PA (97). The exact reasons for a sedentary lifestyle or decreased EC are unknown. An interesting hypothesis is that having impaired physical fitness may imply that sustaining daily activities takes a great deal of effort, resulting in a feeling of exhaustion. In turn this feeling might result in a sedentary lifestyle and ongoing loss of EC.

In general, physical activity has a positive effect on blood pressure, obesity, and bone mineral density (99), and, for patients with JIA, PA seems to have the same health benefits as compared to healthy children. So long-term consequences of a sedentary lifestyle could be that children lose these health benefits, while the disease itself causes potential long-term health risks (35–38). Bar-or formulated a schematic interplay between disease-related and psychosocial factors leading to hypoactivity and subsequently ending in a vicious circle of hypoactivity, deconditioning, and disability (Figure 3) (100).

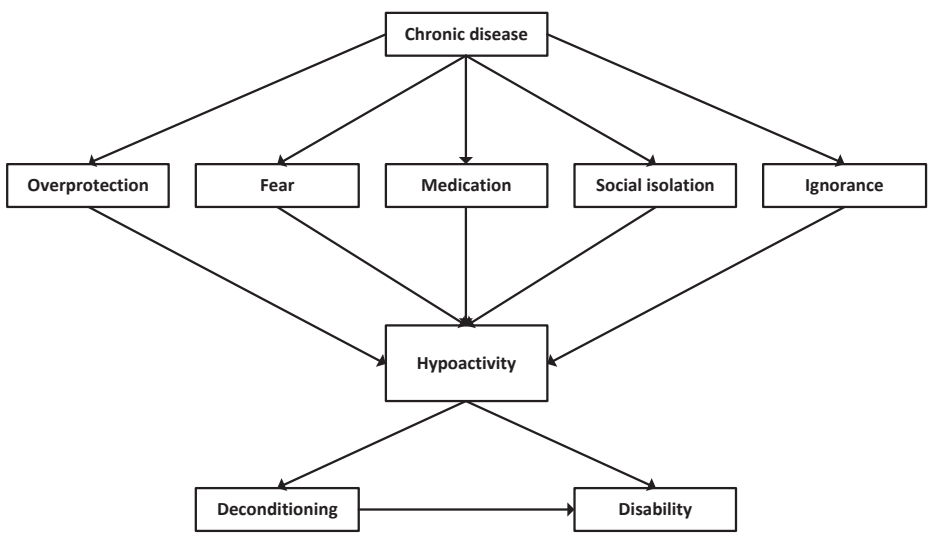

Figure 3. Relationship between chronic disease, hypoactivity, and deconditioning by Bar-or (100)

For patients with JIA, this theory would seem logical, with commonly observed overprotection and lack of knowledge of the disease in parents, teachers, and family. Fear that exercise will cause relapse of the disease is still quite common, although PA has proven to be safe, even in active disease (101). Note that well into the 1980s, absolute bed rest was official medical advice (6). The first step towards preventing patients from becoming inactive is to educate them and their parents about the short- and long-term

benefits of PA, and to assure them that PA is safe, even with active disease. Joint effort is needed to develop interventions to activate patients with JIA. This was the rationale for our study to promote PA in patients with JIA by means of an Internet-based intervention named Rheumates@work.

Health-related Quality of Life

In 2000 Health-related Quality of Life (HRQoL) was recognized as an important focus not only for clinical purposes but also as an outcome measurement in research. The PRINTO network of pediatric rheumatology centers has validated the Childhood Health Questionnaire (CHQ), which measures HRQoL, in many languages including Dutch (51,52). Patients with JIA frequently report a lowered HRQoL regardless of disease activity (80,102–105); however, normal HRQoL has also been reported in children with inactive disease (75). Different factors are recognized that influence HRQoL negatively, such as a polyarticular and systemic subtype, adolescence, disease duration, functional disability, fatigue, pain, subjective burden of medication use, and school absenteeism (104,106,107).

The burden of living with JIA from the patient's perspective

Tong and colleagues published a thematic synthesis of qualitative studies on children's experience in living with JIA (76). Twenty-seven studies from more than 542 participants were reviewed. Six major themes were identified, which the authors presume to be linked. First, JIA patients have an aversion to being different, which is similar to their healthy peers. Constant pain, disablement, perceived internal disfigurement, being treated differently, and being forced to depend on others made them feel different. Second, these patients strive for normality and do not want to be labeled as a sick person. Patients are creative in participating in a range of activities, and they search for interactions with other people with arthritis. Third, JIA patients feel misunderstood especially due to the invisible pain. They feel stigmatized, resulting in limitations in their vocational and career opportunities. Fourth, these patients experience feeling suspended in uncertainty due to the unpredictable nature of the disease. Fifth, the management of the disease is important with respect to taking medicine and involvement with healthcare, along with motivation for physical therapy. Finally, patients have a desire for knowledge regarding medical treatment and lifestyle management. The authors concluded that information was needed about the disease, lifestyle, and treatment; social support and shared decision-making is also needed for the patient in order to improve self-management skills and coping.

JIA affects more or less all components of the ICF model (Figure 2): body function and structure, activities, participation, and environmental factors. Some patients with JIA seem to be more affected by the consequences of JIA than others, with respect to parameters such as disability, pain, fatigue, mood disturbances, low participation, decreased HRQoL, and problems in social relationships. These parameters appear to be correlated more with each other than with disease activity or damage. An intriguing question is why some patients are so incapacitated by their disease, while others with similar disease severity live a full and active life. Little is known about the resilience factors

that contribute to adjustment to the disease; for example, personal factors such as self-efficacy vis-à-vis the disease and self-management skills.

Self-efficacy

Self-efficacy refers to "beliefs in one's capabilities to organize and execute the course of action required to produce given attainments" (108). In children with JIA, the role of self-efficacy in the perception of disease-related factors, like fatigue in JIA, has not been studied (109). The role of self-efficacy was established as a factor for predicting pain in patients with JIA (110). In adults, low self-efficacy for managing pain contributed to predictions of depression, and has been associated with poorer physical and psychological functioning (111,112). Self-efficacy can be enhanced leading to better self-management strategies; self-efficacy could therefore be an important target for interventions. Before this can be applied, the role of self-efficacy in patients with JIA in terms of patient-reported outcome should be ascertained.

Treatment options for JIA have now improved and, as a result, so has the prognosis. Despite this, patient-reported outcome is still impaired in a number of patients with JIA, irrespective of disease activity and severity. More research is needed to recognize those patients at risk for such an impaired outcome and to reveal the underlying mechanisms that lead to resilience in one patient and the lack of it in another. With this knowledge, interventions can be developed.

AIMS OF THIS THESIS

The studies we describe in this thesis are to evaluate patients' perceptions of the disease so as to reveal the consequences of JIA on a patient's daily life and on a patient's self-concept and to understand why some patients are more affected in their daily functioning than others. Furthermore, the effects of a multicenter randomized controlled intervention trial to improve PA in children with JIA will be studied.

The **first chapter** presents an historical outline of all aspects of juvenile idiopathic arthritis, and the progress that has been made in revealing pathophysiological mechanisms and determining treatment strategies. The problems that patients with JIA must face in daily life, such as fatigue and pain, are discussed, as are the theories behind possible psychosocial and self-management interventions. In the **second chapter**, we examine patients' perception of their disease status in relation to the disease assessment of the physician. In the **third chapter**, we study socioeconomic outcome, relationship status, history, and sexual history of young people with JIA compared to healthy controls. We explore satisfaction with relationship status, sexuality, and level of satisfaction with their body, and connection with their body. The associations between body issues (body image and body dissociation) and sexual and status satisfaction will be studied here; and finally, we examine whether pain due to the illness is related to all outcomes among patients with JIA in order to identify those at risk for negative social and sexual outcomes. The **forth chapter** provides a review of current knowledge about fatigue in patients with JIA. We discuss different measurements and we give an overview of the possible causes of

fatigue and the impact it has on daily life. In **chapter five**, we analyze fatigue in 80 patients. Different predictors (disability, pain, exercise capacity, physical activity, disease activity, and medication) of fatigue and possible consequences (school attendance, participation in physical education classes and sports) are studied. In addition, we examine whether self-efficacy moderates the interplay between the causes and consequences. **Chapter six** provides an outline of how PA might be measured in patients with JIA. A seven-day activity diary is compared with an accelerometer (Actical); pros and cons are discussed regarding the practical use of these two measurements. Recommendations are made regarding the duration of registration in PA in order to provide a reliable conclusion about the PA level of patients with JIA. In **chapter seven**, the design and background of Rheumates@work, a combined Internet-based and in-person instruction model, interactive, educational, and cognitive behavioral program for children with juvenile idiopathic arthritis are explained. Acceptance and experience of the participants are also presented. **Chapter eight** presents the results of the multicenter randomized control trial Rheumates@work on physical activity outcome parameters and on Health-related Quality of Life. **Chapter nine** comprises a general discussion.

We conclude that assessing patient-reported outcome is of great importance, while patients perceptions regarding the disease, perceived health, and psychosocial issues do not correspond with disease activity as assessed by the physician. To improve psychosocial outcome, interventions need to be developed aimed at enhancing self-efficacy and self-management strategies that address knowledge, communication adherence, disease-related symptoms (pain and fatigue), and lifestyle changes (including enhancing physical-activity levels).

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